CADTH CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION

MIFEPRISTONE AND MISOPROSTOL
(Mifegymiso — Celopharma Inc.)
Indication: Medical Termination of Pregnancy

Recommendation:
The CADTH Canadian Drug Expert Committee (CDEC) recommends that mifepristone and misoprostol be reimbursed for medical termination of a developing intrauterine pregnancy.

Reasons for the Recommendation:
1. Two randomized controlled trials (RCTs) demonstrated that the regimen of 200 mg oral mifepristone followed by 800 mcg buccal misoprostol 24 to 72 hours later was statistically significantly superior to 200 mg oral mifepristone followed by 800 mcg oral misoprostol (96% versus 91%; $P < 0.048$) and to 1,600 mcg misoprostol alone (93% versus 78%; $P < 0.001$) at inducing complete abortion without surgical intervention at any time in women of child-bearing age with gestational age up to 63 days. Two additional RCTs and one single-group prospective study also provided evidence that mifepristone and misoprostol are associated with successful complete abortion (95% to 97% success rates).
2. Adverse events were experienced by the majority of women in the studies, but these were consistent with the known effects of prostaglandins (e.g., nausea, vomiting, diarrhea, thermoregulatory symptoms). There were no deaths or withdrawals due to adverse events reported in any of the included studies, and serious adverse events were reported in only one study; however, the study durations were shorter than six weeks.

Of Note:

CDEC noted that the patient population included in the studies had gestational age up to 56 to 63 days. The current indication approved by Health Canada is for gestational age up to 49 days. However, the manufacturer has submitted a supplemental new drug submission to Health Canada to extend the gestational age up to 63 days.

Discussion Points:
CDEC discussed the following:

- Mifepristone plus misoprostol provides the only Health Canada–approved option for medical abortion in Canada.
- CDEC discussed that a cost-minimization analysis, as submitted by the manufacturer, may not fully capture benefits of mifepristone plus misoprostol.

Background:
Mifepristone and misoprostol (Mifegymiso) is indicated for medical termination of a developing intrauterine pregnancy with a gestational age of up to 49 days as measured from the first day of the last menstrual period (LMP) in a presumed 28-day cycle. The product monograph recommends a single dose of 200 mg of mifepristone taken orally under supervision of the prescriber or as directed by the prescriber, followed by 800 mcg of misoprostol (four tablets of 200 mcg each) in a single intake by the buccal route 24 to 48 hours (1 to 2 days) later. Mifegymiso is supplied as a single 200 mg mifepristone tablet and four 200 mcg misoprostol tablets boxed separately and packaged together.

Summary of CDEC Considerations:
CDEC considered the following information prepared by the CADTH Common Drug Review (CDR): a systematic review of phase III RCTs and pivotal trials identified by the manufacturer of mifepristone and misoprostol, and a critique of the manufacturer's pharmacoeconomic evaluation.

Patient Input Information
No patient submissions were received in response to the Call for Patient Input.

Clinical Trials
The CDR systematic review included five prospective trials conducted in females of child-bearing age seeking medical abortion. Three open-label trials were considered to be pivotal. Study 1 (N = 442), Study 2 (N = 966), and Study 3 (N = 1,000). Two double-blind trials were identified from the clinical literature search: Study 4 (N = 90) and Study 5 (N = 441). Three trials (Studies 1, 2 and 4) were randomized, parallel-group comparisons of different routes of administration of misoprostol (i.e., buccal compared with oral, vaginal, and sublingual [SL], respectively), all following a single oral dose of mifepristone. Study 5 was a randomized trial that compared oral mifepristone plus buccal misoprostol with buccal misoprostol alone. Randomization was not stratified by any variables in the trials. Study 3 was a non-randomized, single-group trial. The trials enrolled females aged 14 years and older who were voluntarily seeking medical abortion with gestational age of 56 to 63 days since LMP. In all the trials, a subpopulation of females with pregnancies $\leq$ 49 days gestation based on LMP (as per the Health Canada–approved indication for Mifegymiso) could be identified.

Key limitations of the available evidence are the lack of direct comparison with surgical abortion or methotrexate/misoprostol, which are the currently used methods in Canada (methotrexate/misoprostol use is off-label); uncertainty about whether the subgroups reported in the trials were pre-specified; lack of stratification by gestational age; and lack of control or adjustments of secondary outcomes for multiplicity.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, CDEC discussed the following:

- Pregnancy outcome (i.e., complete abortion successes, failures, and reasons for failures).
- Patient satisfaction (which was compared statistically only in Study 5).
- Complication rates (i.e., based on patients' expectations of bleeding and pain). No statistical comparisons were conducted between groups for this outcome in any of the trials.

The primary outcome in Studies 1, 2, 3, and 5 was complete abortion without surgical intervention at any time. In Study 4, the primary outcome was the proportion of women with fever (> 38°C), but a secondary outcome was complete abortion. The included trials did not report any results pertaining to health-related quality of life, psychiatric/psychological morbidity, or health care resource utilization, which were other efficacy outcomes identified in the protocol.

Efficacy

- Success rates (i.e., the proportion of women with complete abortion without surgical intervention at any time) were:
  - Study 1: Mifepristone plus misoprostol buccal versus vaginal: 94.9% versus 93.4% (*P* = 0.51)
  - Study 2: Mifepristone plus misoprostol buccal versus oral: 96.2% versus 91.3% (*P* < 0.048)
  - Study 3: Mifepristone plus misoprostol buccal (97.3%)
  - Study 4: Mifepristone plus misoprostol buccal versus SL: 95.6% versus 97.8% (*P* = not significant)
  - Study 5: Mifepristone plus misoprostol buccal versus misoprostol buccal alone: 92.9% versus 78.0% (*P* < 0.001).
- Overall patient satisfaction, n (%)
  - Study 1: Mifepristone plus misoprostol buccal versus vaginal: 92.0% versus 94.7%
  - Study 2: Mifepristone plus misoprostol buccal versus oral: 91.1% versus 92.6%
  - Study 3: Mifepristone plus misoprostol buccal: 94.4%
  - Study 5: Mifepristone plus misoprostol buccal versus misoprostol buccal alone: relative risk for “very satisfied:” 0.75 (95% CI, 0.59 to 0.96) (*P* = 0.020).
- Complication rates: In Studies 2, 3, and 5, patients' expectations regarding the amount of bleeding and pain was reported as “less than expected,” “same as expected,” or “more than expected” and results were as follows, n (%):
  - Study 2: Mifepristone plus misoprostol buccal versus vaginal: Bleeding was 28.9% versus 28.3%/43.6% versus 44.0%/29.9% versus 26.0%; and pain was 29.6% versus 38.6%/38.8% versus 34.3%/29.9% versus 25.7%.
  - Study 3: Mifepristone plus misoprostol buccal: Bleeding was 30.5%/41.7%/27.0%; and pain was 26.3%/26.9%/46.0%, respectively.
  - Study 5: Mifepristone plus misoprostol buccal versus misoprostol alone: Bleeding was 34.0% versus 26.7%/35.4% versus 30.1%/30.6% versus 43.2%; and pain was 31.9% versus 33.2%/25.0% versus 22.6%/43.1% versus 44.2%.

Harms (Safety and Tolerability)

- No deaths were reported in any of the trials.

- The proportion of patients with at least one serious adverse event was reported only in Study 3. In total, 11 patients (1.1%) experienced a serious adverse event which primarily included heavy bleeding, fainting, and lower abdominal pain requiring hospitalization and dilation and curettage.
- No patients withdrew due to adverse events in any of the trials.
- The proportion of patients who experienced at least one treatment-emergent adverse event (TEAE) was reported only in Study 2 and Study 3. The proportion of patients with TEAEs in Study 2 was 94.9% (mifepristone oral plus misoprostol buccal) and 97.3% (mifepristone oral plus misoprostol oral) and in Study 3 was 88.5% (mifepristone oral plus misoprostol buccal).
- The most frequently reported TEAEs across all trials were nausea, vomiting, diarrhea and fever/chills which generally occurred with similar frequency between treatment groups in individual trials. In Study 4, more patients in the misoprostol SL group experienced nausea (60.0%), vomiting (33.3%), and fever/chills (91.1%) compared with the misoprostol buccal group (i.e., 46.7%, 20.0%, and 55.6%, respectively). In Study 5, diarrhea occurred more frequently in patients in the misoprostol buccal alone group (83.9%) compared with the mifepristone oral and misoprostol buccal group (61.2%).

Cost and Cost-Effectiveness

Mifepristone and misoprostol is available at a manufacturer-submitted price of $300 for a single kit (consisting of one 200 mg tablet of mifepristone and four 200 mcg tablets of misoprostol).

The manufacturer submitted a cost-minimization analysis comparing mifepristone plus misoprostol with methotrexate plus misoprostol, vacuum aspiration in hospital, and vacuum aspiration in a free-standing clinic for pregnant women with up to 63 days of gestation. The manufacturer's analysis was based on a decision tree that captured treatment success and complications (i.e., excess bleeding, infection). By the end of the model, pregnancy was considered terminated in all patients regardless of the initial abortion strategy. Under a health care system perspective, the manufacturer reported a total average cost for mifepristone plus misoprostol of $582.56, which was $201.87 more than methotrexate plus misoprostol, and $79.42 more than vacuum aspiration in clinic, but $445.97 less than vacuum aspiration in hospital.

CDR identified several limitations with the manufacturer's analysis, that included: a cost-minimization analysis assumes that all relevant clinical differences between abortion regimens can be accounted for in costs; the study population modelled was broader than the Health Canada indication; the off-label misoprostol alone regimen was not considered; most of the probabilities in the manufacturer's model could not be validated; and there were no head-to-head comparisons against its comparators. Resource utilization in the model did not reflect current clinical practice and the approach taken to adjust costs was not appropriate.

CDR performed a re-analysis to address the limitations, where possible, by: revising pricing based on current fee schedules; employing validated probabilities; changing the resource utilization to reflect Canadian practice patterns; and including a misoprostol alone comparison. These revised assumptions resulted in a CDR reference case of $610 for mifepristone plus misoprostol, which was $89 more expensive than surgical abortion by vacuum aspiration in clinic but $916 less expensive than vacuum aspiration in hospital. Mifepristone plus misoprostol was more expensive compared with other medical options that are not currently approved by Health Canada for this indication ($200 more expensive than a methotrexate plus misoprostol regimen and $77 more expensive than misoprostol alone).

CDEC Members:
Dr. Lindsay Nicolle (Chair), Dr. James Silvius (Vice-Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Mr. Frank Gavin, Dr. Peter Jamieson, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. Adil Virani, and Dr. Harindra Wijeysundera.

March 15, 2017 Meeting

Regrets:
None

Conflicts of Interest:
None

About this Document:
CDEC provides formulary listing recommendations or advice to CDR participating drug plans. CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC deliberated on a review and made a recommendation or issued a record of advice. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has not requested the removal of confidential information.

The CDEC recommendation or record of advice neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

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